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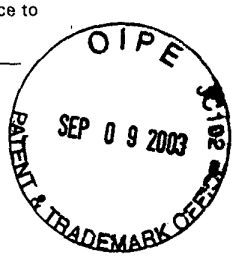

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Appl. No.:	09/717,450		
Applicant:	Lisa A. Neuhold and Loran Marie Killar	G.A.U.:	1632
Filed:	November 20, 2000	Examiner:	Michael C. Wilson
Title	Transgenic Animal Model for Degenerative Diseases of Cartilage		
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COURTESY COPY OF PENDING CLAIMS

Sir:

Claims 1-54 (Cancelled)

Claim 55 (Currently Amended): A transgenic non-human mammal whose genome comprises:

(a) a nucleotide sequence encoding a constitutively enzymatically active human matrix metalloproteinase that cleaves Type II collagen, wherein the nucleotide sequence encoding the metalloproteinase is operatively linked to a regulatable promoter; and

(b) a nucleotide sequence encoding a repressor-activator fusion polypeptide that binds to the regulatable promoter in the absence of a repressor-activator fusion polypeptide-binding compound and does not bind to the regulatable promoter in the presence of the compound, which nucleotide sequence encoding the repressor-activator fusion polypeptide is operatively linked to a joint-specific promoter,

wherein expression of the metalloproteinase is capable of being repressed in the mammal until adulthood, and wherein the metalloproteinase is capable of being expressed in the mammal during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the mammal.

Claim 56 (Previously Presented): The transgenic mammal of claim 55, wherein the matrix metalloproteinase is selected from the group consisting of MMP-1, MMP-8, and MMP-13.

Claim 57 (Previously Presented): The transgenic mammal of claim 56, wherein the matrix metalloproteinase is MMP-13.

Claim 58 (Cancelled)

Claim 59 (Currently Amended): The transgenic mammal of claim 57, wherein the MMP-13 comprises the sequence of SEQ ID NO: 1 or SEQ ID NO: 21.

Claim 60 (Previously Presented): The transgenic mammal of claim 55, wherein the repressor-activator fusion polypeptide is a chimeric tetracycline repressor-VP16 transcription activator polypeptide and the regulatable promoter is a Tn10 sequence linked to a portion of the CMV IE promoter.

Claim 61 (Previously Presented): The transgenic mammal of claim 60, wherein the regulatable promoter comprises the sequence of SEQ ID NO: 2.

Claim 62 (Previously Presented): The transgenic mammal of claim 55, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 63 (Currently Amended): The transgenic mammal of claim 55, wherein the joint-specific promoter is a Type II collagen promoter.

Claim 64 (Currently Amended): A transgenic rat whose genome comprises:

(a) a nucleotide sequence encoding a constitutively enzymatically active human matrix metalloproteinase that cleaves Type II collagen, wherein the nucleotide sequence encoding the metalloproteinase is operatively linked to a tetracycline-regulatable promoter; and

(b) a nucleotide sequence encoding a repressor-activator fusion polypeptide that binds to the tetracycline regulatable promoter in the absence of tetracycline or a tetracycline analog and does not bind to the regulatable promoter in the presence of tetracycline or tetracycline analog, which nucleotide sequence encoding the repressor-activator fusion polypeptide is operatively linked to a joint-specific promoter,

wherein expression of the metalloproteinase is capable of being repressed in the rat until adulthood, and wherein the metalloproteinase is capable of being expressed in the rat during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the rat.

Claim 65 (Currently Amended): The transgenic rat of claim 64, wherein the matrix metalloproteinase is constitutively enzymatically active MMP-13, the tetracycline-regulatable promoter is tet07, the repressor-activator fusion polypeptide is tTA, and the joint-specific promoter is a Type II collagen promoter.

Claim 66 (Previously Presented): The transgenic rat of claim 64, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 67 (Previously Presented): A method for producing degradation of Type II collagen in the joints of a transgenic non-human mammal, which method comprises:

(a) maintaining the transgenic mammal of claim 55 in presence of the transcription activator protein-binding compound until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic mammal by withholding the compound from the mammal after the mammal has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the transgenic mammal.

Claim 68 (Previously Presented): The method according to claim 67, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 69 (Currently Amended): A method for producing degradation of Type II collagen in the joints of a transgenic non-human mammal, which method comprises:

(a) maintaining the transgenic mammal of claim 60 in the presence of tetracycline or a tetracycline analog until adulthood; and

(b) activating expression of the matrix metalloproteinase by withholding the tetracycline or tetracycline analog from the mammal after the mammal has reached adulthood,

such that the matrix metalloproteinase degrades Type II collagen in the joints of the transgenic mammal.

Claim 70 (Previously Presented): The method according to claim 69, wherein the tetracycline analog is doxycycline.

Claim 71 (Previously Presented): The method according to claim 69, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 72 (Previously Presented): A method for producing degradation of Type II collagen in the joints of a transgenic rat, which method comprises

(a) maintaining the transgenic rat of claim 64 in the presence of tetracycline or a tetracycline analog until adulthood; and

(b) activating expression of the matrix metalloproteinase by withholding the tetracycline or tetracycline analog from the rat after the rat has reached adulthood, such that the matrix metalloproteinase degrades Type II collagen in the joints of the transgenic rat.

Claim 73 (Previously Presented): The method according to claim 72, wherein the tetracycline analog is doxycycline.

Claim 74 (Previously Presented): The method according to claim 72, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 75 (Currently Amended): A transgenic non-human mammal whose genome comprises:

(a) a nucleotide sequence encoding a constitutively enzymatically active human matrix metalloproteinase that cleaves Type II collagen, wherein the nucleotide sequence encoding the metalloproteinase is operatively linked to a regulatable promoter; and

(b) a nucleotide sequence encoding a transcription activator protein that binds to the regulatable promoter in the presence of a transcription activator protein-binding compound and does not bind to the regulatable promoter in the absence of the compound, which nucleotide sequence encoding the transcription activator protein is operatively linked to a joint-specific promoter;

wherein expression of the metalloproteinase is capable of being repressed in the mammal until adulthood, and wherein the metalloproteinase is capable of being expressed in the mammal during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the mammal.

Claim 76 (Previously Presented): The transgenic mammal of claim 75, wherein the matrix metalloproteinase is selected from the group consisting of MMP-1, MMP-8, and MMP-13.

Claim 77 (Previously Presented): The transgenic mammal of claim 76, wherein the matrix metalloproteinase is MMP-13.

Claim 78 (Cancelled)

Claim 79 (Currently Amended): The transgenic mammal of claim 77, wherein the MMP-13 comprises the sequence of SEQ ID NO: 1 or SEQ ID NO: 21.

Claim 80 (Currently Amended): The transgenic mammal of claim 75, wherein the joint-specific promoter is a Type II collagen promoter.

Claim 81 (Currently Amended): The transgenic mammal of claim 75, wherein the transcription activator protein is a chimeric polypeptide comprising a transactivator domain linked to an ecdysone receptor ligand-binding domain, and wherein the transgenic mammal further comprises a nucleotide sequence encoding a retinoid X receptor (RXR), which nucleotide sequence encoding RXR is operatively linked to a joint-specific promoter.

Claim 82 (Previously Presented): The transgenic mammal of claim 75, wherein the transcription activator protein is a chimeric polypeptide comprising a transactivator domain linked to a progesterone receptor ligand-binding domain.

Claim 83 (Previously Presented): The transgenic mammal of claim 75, wherein the transcription activator protein is a chimeric polypeptide comprising a transactivator domain linked to a steroid binding domain.

Claim 84 (Previously Presented): The transgenic mammal of claim 75, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 85 (Previously Presented): A method for producing degradation of Type II collagen in the joints of a transgenic non-human mammal, which method comprises:

(a) maintaining the transgenic mammal of claim 75 in the absence of the transcription activator protein-binding compound until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic mammal by administering the compound to the mammal after the mammal has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the mammal.

Claim 86 (Previously Presented): A method for producing degradation of Type II collagen in the joints of a transgenic non-human mammal, which method comprises:

(a) maintaining the transgenic mammal of claim 81 in the absence of ecdysone, an ecdysone analog, or dexamethasone until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic mammal by administering ecdysone, an ecdysone analog, or dexamethasone to the mammal after the mammal has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the mammal.

Claim 87 (Previously Presented): A method for producing degradation of Type II collagen in the joints of a transgenic non-human mammal, which method comprises:

(a) maintaining the transgenic mammal of claim 82 in the absence of mifeprestone (RU 486) until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic mammal by administering mifepristone (RU 486) to the mammal after the mammal has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the mammal.

Claim 88 (Previously Presented): The method according to claim 86, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 89 (Previously Presented): The method according to claim 87, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 90 (Currently Amended): A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a non-human transgenic mammal, which method comprises:

(a) administering the composition to the transgenic mammal of claim 55 in which a phenotypic change has been produced by activation of expression of the metalloproteinase during adulthood of the transgenic mammal, wherein the phenotypic change is selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof; and

(b) comparing the extent of the phenotypic change in the mammal to which the composition was administered with that of a control transgenic mammal in which the composition was not administered but expression of the

metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered,

wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for the phenotypic change to develop in the mammal that has been administered the composition relative to the control mammal, indicates the potential of the composition to counteract the degradation of Type II collagen in joints of the mammal.

Claim 91 (Currently Amended): A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a non-human transgenic mammal, which method comprises:

(a) administering the composition to the transgenic mammal of claim 60 in which a phenotypic change has been produced by activation of expression of the metalloproteinase during adulthood of the transgenic mammal, wherein the phenotypic change is selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof; and

(b) comparing the extent of the phenotypic change in the mammal to which the composition was administered with that of a control transgenic mammal in

which the composition was not administered but expression of the metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered,

wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for the phenotypic change to develop in the mammal that has been administered the composition relative to the control mammal, indicates the potential of the composition to counteract the degradation of Type II collagen in the joints of the mammal.

Claim 92 (Currently Amended): A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a transgenic rat, which method comprises:

(a) administering the composition to the transgenic rat of claim 64 in which a phenotypic change has been produced by activation of expression of the metalloproteinase during adulthood of the transgenic rat, wherein the phenotypic change is selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof; and

(b) comparing the extent of the phenotypic change in the rat to which the composition was administered with that of a control transgenic rat in which the composition was not administered but expression of the metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered,

wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for the phenotypic change to develop in the rat that has been administered the composition relative to the control rat, indicates the potential of the composition to counteract the degradation of Type II collagen in the joints of the mammal.

Claim 93 (Currently Amended): A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a non-human transgenic mammal, which method comprises:

(a) administering the composition to the transgenic mammal of claim 75 in which a phenotypic change has been produced by activation of expression of the metalloproteinase during adulthood of the transgenic mammal, wherein the phenotypic change is selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth

plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof; and

(b) comparing the extent of the phenotypic change in the mammal to which the composition was administered with that of a control transgenic mammal in which the composition was not administered but expression of the metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered,

wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for the phenotypic change to develop in the mammal that has been administered the composition relative to the control mammal, indicates the potential of the composition to counteract the degradation of Type II collagen in the joints of the mammal.

Claim 94 (Currently Amended): A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a non-human transgenic mammal, which method comprises:

(a) administering the composition to the transgenic mammal of claim 81 in which a phenotypic change has been produced by activation of expression of the metalloproteinase during adulthood of the transgenic mammal, wherein the phenotypic change is selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint

function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof; and

(b) comparing the extent of the phenotypic change in the mammal to which the composition was administered with that of a control transgenic mammal in which the composition was not administered but expression of the metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered,

wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for the phenotypic change to develop in the mammal that has been administered the composition relative to the control mammal, indicates the potential of the composition to counteract the degradation of Type II collagen in the joints of the mammal.

Claim 95 (Currently Amended): A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a non-human transgenic mammal, which method comprises:

(a) administering the composition to the transgenic mammal of claim 82 in which a phenotypic change has been produced by activation of expression of the metalloproteinase during adulthood of the transgenic mammal, wherein the phenotypic change is selected from the group consisting of loss of proteoglycan,

cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof; and

(b) comparing the extent of the phenotypic change in the mammal to which the composition was administered with that of a control transgenic mammal in which the composition was not administered but expression of the metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered,

wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for the phenotypic change to develop in the mammal that has been administered the composition relative to the control mammal, indicates the potential of the composition to counteract the degradation of Type II collagen in the joints of the mammal.

Claim 96 (Currently Amended): A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a non-human transgenic mammal, which method comprises:

(a) administering the composition to the transgenic mammal of claim 83 in which a phenotypic change has been produced by activation of expression of the metalloproteinase during adulthood of the transgenic mammal, wherein the

phenotypic change is selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC^A degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof; and

(b) comparing the extent of the phenotypic change in the mammal to which the composition was administered with that of a control transgenic mammal in which the composition was not administered but expression of the metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered,

wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for the phenotypic change to develop in the mammal that has been administered the composition relative to the control mammal, indicates the potential of the composition to counteract the degradation of Type II collagen in the joints of the mammal.